GP- 1648
#19 4/4/00 TBM
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Sastry, et al.

Serial No.: 08/869,386

Filed: June 5, 1997

For: COMPOSITIONS AND METHODS FOR ELICITING AN IMMUNE RESPONSE

Group Art Unit: 1648

Examiner: B. Nelson

Atty. Dkt. No.: UTSC:538/HAS

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APPEAL BRIEF

BOX AF
Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Appellants hereby submit an original and two copies of this Appeal Brief to the Board of Patent Appeals and Interferences in response to the Final Office Action dated September 28, 1999. The two-month date for filing an Appeal Brief was March 6, 2000. Therefore, pursuant to 37 C.F.R. § 1.136(a), Applicants include herewith a petition for an extension of time of one month, bringing the due date to April 6, 2000. Pursuant to 37 C.F.R. § 1.17, a check in the amount of ($205.00) is enclosed, which includes the process fee ($55.00) for a one-month extension of time and the fee for filing the Appeal Brief ($150.00).

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I. REAL PARTY IN INTEREST

This application has been assigned to the Board of Regents, University of Texas System (Reel/Frame 6371/0957) and is licensed to BioQuest Inc.

II. RELATED APPEALS AND INTERFERENCES

The parent case of this application, U.S. Ser. No. 07/945,865, from which this application is a divisional, is currently the subject of an appeal. An appeal brief was filed in the '865 application on July 19, 1995. In addition, the '865 application was a continuation-in-part of U.S. Serial No. 07/800,932 ("the '932 application"). An appeal brief was filed in the '932 application on November 17, 1994.

III. STATUS OF THE CLAIMS

Claims 1-28 were filed with the original application. Claims 1-28 were canceled in the preliminary amendment and claims 29-48 added. Claim 46 and 48 were canceled during the prosecution of the application. Claims 29-45, 47 and 49 were pending at the time of the final Office Action. Claims 29-45, 47 and 49 were rejected by the action. An amendment to Claim 47 has been submitted with this appeal and it is respectfully requested that it be entered. Claims 29-45, 47 and 49 are currently pending and are appealed. The claims are reproduced in Appendix A.

IV. STATUS OF AMENDMENTS

Claim 47 has been amended in a concurrent amendment submitted as Appendix B to correct an improper dependency from a canceled claim.

A substitute specification is included as Appendix C to comply with examiner's objection to the current specification.

V. SUMMARY OF THE INVENTION

The present invention relates in a general sense to a method for directly inhibiting HIV virion entry into the cells of a host organism. Specification at page 12, lines 22-27. More specifically, the invention involves methods of contacting a cell within an individual with the disclosed peptides in order to inhibit the ability of the human immunodeficiency virus to infect the cell. Specification at page 57, lines 13-20.

VI. ISSUES ON APPEAL

The issues on appeal are:

A. Does the specification of the '386 application fail to provide enablement commensurate with the scope of the claims as currently pending?

B. Is claim 49 anticipated by the Berzofsky *et al.* reference?

VII. GROUPING OF THE CLAIMS

The claims stand or fall together with regards to the §112 rejection. The claim 49 stands alone with regard to the §102 rejection, which is independently argued.

VIII. SUMMARY OF THE ARGUMENT

Claims 29-45, 47 and 49 are fully enabled by the '386 specification. The working examples set forth in the specification provide enablement commensurate with the scope of protection sought by the appellants. Subsequent *in vivo* data in an accepted model system and the ability of others to use peptide therapeutics in an analogous fashion provide further

corroboration that the specification is adequately enabling. The PTO's arguments to the contrary are in error or wholly lack merit.

The Berzofsky *et al.* reference fails to anticipate claim 49 either expressly or inherently. The cited prior art reference fails to expressly include all of the elements of the claim invention and thus cannot expressly anticipate the subject matter of claim 49. The reference further fails to teach that the processes disclosed therein would result in anything more than the initiation of an immune response against viral antigens and is thus also inadequate to inherently anticipate the claimed invention. The PTO is therefore incorrect in its assertion that the instant application is anticipated by the cited reference.

IX. ARGUMENT

A. CLAIMS 29-45, 47 AND 49 ARE FULLY ENABLED BY THE '386 SPECIFICATION.

According to the Action, the claims are overly broad in light of the disclosure provided by the specification. The PTO asserts that, while the specification is enabled under 35 U.S.C. §112 for a method of inhibiting HIV entry into a cell *in vitro*, the specification does not provide enablement for a method of inhibiting HIV entry into a cell *in vivo*. The PTO bases its enablement rejection on a lack of correlation between the *in vitro* data presented and the scope of the claims. Appellants respectfully traverse the rejection.

Appellants concur with the PTO's assertion that the claims currently recite a method for directly inhibiting viral entry into cells. Appellants further agree that the claims do not necessarily recite a means of directly inhibiting the progression of the disease insofar as such an inhibition is not directly related to a limitation of subsequent viral infection due to the action of the peptide. The claims may, however, be broadly construed to recite a method of protecting

human cells from infection. This construction is completely in line with the teaching of the specification and the declarations submitted by Dr. Arlinghaus.

The specification of the '386 application teaches a method of introducing the claimed peptides into a host organism, wherein these peptides function to directly inhibit the uptake of HIV virions by the host's cells. The efficacy of this method is confirmed in the specification by *in vitro* data demonstrating that the claim peptides effectively inhibit viral entry into human cells. Subsequent *in vivo* data relating experiments in chimpanzees demonstrate that the introduction of the peptide effectively reduces viral titer in the host (provided to the PTO in a declaration by applicant, Dr. Arlinghaus) which corroborates the effects seen *in vitro*.

The *in vitro* data provided by the specification, when read in light of the subsequent supporting declaration correlates with the scope of the claims as presently submitted. Correlation as defined in MPEP 2164.02:

> refers to the relationship between *in vitro* or *in vivo* animal model assays and a disclosed or a claimed method of use. An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. If there is no correlation, then the examples do not constitute "working examples." In this regard, the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate.

The *in vitro* data presented in the application demonstrates that peptides of the invention inhibit viral infection of individual cells. When read in light of the subsequent declaration, these results are further adequate to demonstrate that the peptide effectively inhibits viral uptake in a host organism as well. The correspondence between the efficacy of the peptides *in vivo* with the *in vitro* data presented by the specification provides "relevant evidence as a whole, [that] there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity." *Cross v.*

Iizuka, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985). A more rigorous correlation is not necessary because the pharmacological activity claimed is reasonably based upon the specification's working examples in light of the additional probative evidence submitted. *See id.*

1. The Action's Assertion that Chimpanzees are not an Adequate Model for Correlating *In Vivo* Efficacy Of Inhibition of Viral Infectivity is Erroneous

The Action finds that the *in vivo* data from chimpanzees does not correlate with the specification's *in vitro* data because chimpanzees do not represent a valid model of HIV infection. Notwithstanding the PTO's assertion to the contrary, chimpanzees are the accepted model for HIV infection, and are the preferred system for investigating methods of protection. (Fultz, 1993, attached as Appendix D). While chimpanzees do not exhibit the morbidity or mortality seen in humans in response to HIV infection, the virus readily infects chimpanzee T cells in a manner equivalent to that observed in humans. Because of the equivalence of the route of infection, the chimpanzee model, in fact, provides the best system for testing the efficacy of experimental strategies of preventing viral uptake at the cellular level. Therefore, in the context of the present invention, chimpanzees represent the ideal choice for demonstrating the effectiveness of the disclosed peptides in directly inhibiting viral uptake by cells within a host.

The Haynes et al. references cited by the PTO bases its criticism of the chimpanzee model on the failure of chimpanzees to develop the symptoms seen in humans infected with HIV. In the context of the instant invention, it is irrelevant that the model system utilized does not exhibit analogous symptoms in response to infection. The relevant variable is the course of infection rather than the infections ultimate impact. While morbidity may be an important factor in some experimental systems, it is of no importance in evaluating the efficacy of the instant invention.

The nature of the course of infection in chimpanzees allows for the extrapolation from the *in vivo* data cited by the appellants that the claimed peptides inhibit viral entry into cells in a host organism. These data confirm that the peptides function in a manner analogous to that observed in the previous *in vitro* experiments. Thus, due to the equivalence of HIV infectivity in humans and chimpanzees, a person of ordinary skill in the art would expect similar results if the peptide were introduced into a human subject.

2. Peptide Therapeutics Are an Accepted Means of Inhibiting Viral Uptake in HIV Infection

The Action cites Yarchoan and Broder (J. Enz. Inh. 1992) and Gait *et al.* (TIBTECH, 1995) (attached as Appendices E and F) to support its contention that agents shown to block HIV infection of cells lack clinical efficacy and are subject to seemingly insurmountable problems that preclude their *in vivo* use. Nevertheless, in addition to the data provided by the appellants confirming the value of peptide therapeutics *in vivo,* there are a number of studies that reflect that peptides are, in fact, an effective means of inhibiting the infectivity of the virus *in vivo.* These references further demonstrate that a person of ordinary skill would be aware of methods for providing the peptides to a host to effectively inhibit cellular infection. *See e.g.* Vitetta *et al* United States Patent 5,767,072; Sabatier *et al.* United States Patent 5,622,933 (Attached as Appendices G and H). It should be further noted that SPC_3, a peptide closely related to that disclosed in the instant invention, is currently undergoing phase II clinical trials as a means of preventing viral uptake. *See* FDA 257A. Title: Study of the Safety and Effects of Two Doses of SPC3, Administered Daily Intravenously in HIV-1 Seropositive Patients (Attached as Appendix I).

3. The Term "Replication" as Used by Dr. Arlinghaus in His Declaration Equates to An Inhibition of Viral Uptake In Vitro

Dr. Arlinghaus states in his declaration that the introduction of the RK15 peptide inhibits HIV replication *in vivo* and *in vitro*. The PTO counters that the prevention of replication as represented by a decrease in viral titer does not equate to the prevention of infection in the host. While this contention may or may not be true, the term "replication," as employed by Dr. Arlinghaus denotes a representation that an inhibition of cellular infection rather than a prevention of host infection has occurred.

An evaluation of viral titer is used by the applicants to correlate the presence of the peptide with an inhibition of cellular infectivity. An evaluation of viral titer is commonly employed to evaluate the progression of the infection in the host. A lower viral titer in experimental as compared to control organisms reflects a depressed ability of the virus to replicate and in turn to infect cells. Low viral titer, when correlated with the activity of the peptide *in vitro* readily leads to the conclusion that the peptide's efficacy *in vitro* is also exhibited in an infected host.

One of the primary purposes of performing *in vitro* experimentation is that the investigator is readily able to exert a greater degree of control over specific experimental conditions. Conversely, *in vivo* experimentation increases the number of variables that must be considered in reaching any conclusion related to observed results. Where, however, there is a correlation of *in vivo* and *in vitro* results, a researcher is able to reasonably conclude that a specific effect seen *in vitro* will be reproduced in an *in vivo* environment. Therefore, Dr. Arlinghaus' conclusion that a decrease in viral titer correlated to inhibition of cellular infection is warranted.

4. The Action is in Error in Asserting that it would Require Undue Experimentation to Make or Use the Claimed Invention

The PTO gives four reasons that the '386 application would require undue experimentation and is thus not enabling. These factors include: 1) there are no working examples which suggest the desired results of inhibiting HIV infection *in vivo*; 2) the nature of the invention involved the complex and incompletely understood area of immunity [sic] to HIV; 3) the state of the prior art shows that treatment methods have been largely ineffective for the intended purpose; and 4) the lack of predictability in the field to which the invention pertains is recognized in the art as evidenced by the prior failures. As argued *supra*, the working examples provided in the specification adequately correlate with the scope of protection sought. Further, the teaching provided by the specification and specifically the working examples are sufficient to fully enable a person of ordinary skill to make and use the claimed invention as required by 35 U.S.C. §112. This correlation and the nature of the disclosure effectively refutes the PTO's assertions to the contrary.

The teaching of the specification provided with the '386 application adequately enables the scope of the claims as currently drafted. The *in vitro* working examples provided with the specification, when read in light of the subsequent *in vivo* data, correlate with the scope of protection sought by the appellants. Therefore, the PTO's assertion that the '386 specification fails to enable the scope of the claims is in error.

B. THE BERZOFSKY *et al.* REFERENCE FAILS TO ANTICIPATE CLAIM 49 EITHER EXPRESSLY OR INHERENTLY

The PTO rejects claim 49 under 35 U.S.C. §102(a), as anticipated by Berzofsky *et al.* The PTO asserts that Berzofsky discloses a method for protecting cells from HIV comprising administering to mice a composition that comprises a peptide having the claimed sequence, and restimulating the cells again by contacting the cells *in vitro* with the composition. Appellants respectfully traverse this rejection.

1. The Cited Prior Art Reference Fails to Expressly Include all of the Elements of the Claim Invention

Appellants acknowledge that the goal of both the instant application and Berzofsky is the protection of host cells from HIV. Appellants further acknowledge that both the instant application and Berzofsky rely upon a peptide, designated as R15K. However, the mechanisms of protection taught by the instant application and its intended use are quite distinct from those disclosed by Berzofsky.

The protection described in Berzofsky is based upon the induction of a cellular immune response established by the administration of the peptide to a naïve host. Upon administration, cells within the host phagocytize the peptide and process it within their endoplasmic reticulum. In the endoplasmic reticulum, the peptide is associated with MHC class I. The peptide/MHC complex is subsequently surface expressed by the cell. The peptide is recognized as foreign by cytotoxic T lymphocytes (CTL) possessing the proper T cell receptor (TCR) configuration. Upon recognition of the antigen as foreign, the CTL becomes activated and proliferates. This creates a subpopulation of peptide specific CTL able to rapidly control subsequent infection. In the event of a viral infection, this subpopulation can rapidly expand to kill cells infected with the

virus. Cells expressing the viral peptide on their surface are recognized by the CTL subpopulation and either lysed or induced into an apototic state. By eliminating these infected cells, the production of viral particles is inhibited and, ideally, the infection eventually is curtailed or terminated.

In contrast, the instant application encompasses the inhibition of viral uptake through the direct interaction between the claimed peptides and the virus or target cells. The disclosed invention provides a method in which the peptide itself inhibits the entry of the viral particle by directly preventing the interaction between the virion and the cell. In order for the HIV virion to infect a host cell, it must interact with specific molecules on the cells surface. It is contemplated that the peptides disclosed by the instant invention effectively prevent this interaction, thus precluding cellular infection.

Thus, the instant application is not directed towards employing the peptide to elicit an immune response. Rather, the claimed peptide itself directly inhibits the interaction required for the virion to enter the target cell. The fact that the peptide inhibits viral entry rather than a cellular response elicited by the peptide distinguishes the instant application from the cited prior art.

The Federal Circuit has determined that, to support a §102 rejection, the cited prior art reference must contain each limitation of the anticipated claim and enable one skilled in the art to make the anticipated subject matter. *Chester v. Miller*, 906 F.2d 1574, 1576 n.2, 15 U.S.P.Q.2d 1333, 1336 n.2 (Fed. Cir. 1990). Accordingly, even if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it is not sufficiently enabling. *In re Borst*, 345 F.2d 851, 855, 145 U.S.P.Q. 554, 557 (C.C.P.A. 1965), cert. denied, 382 U.S. 973,

86 S.Ct. 537, 15 L.Ed.2d 465 (1966). The phrase "for directly inhibiting HIV entry into cells" in the claims of the instant application envisions a method in which the cells to be protected are contacted with a preparation which, itself, directly inhibits the ability of viral particles to infect the cell. Such a term, even though it appears in the preamble to the claim may be deemed a limitation of the claim when it gives meaning to the claim and properly define the invention. *In re Paulsen*, 30 F.3d 1475, 31 U.S.P.Q.2d 1671 (Fed. Cir. 1994). The claim language of the instant application thus specifically envisions that the inhibition of viral entry results from the peptide itself, rather than a response generated as a result of previous administration of the peptide.

2. The Cited Prior Art does not Inherently Disclose the Subject Matter of the Claimed Invention

The PTO may, alternatively, be basing its rejection on the doctrine of inherent anticipation. However, the Berzofsky patent teaches a method of inducing a CTL response, and one of ordinary skill in the art would not derive from its teachings a means of directly inhibiting viral uptake. It further should be recognized that the methods and means necessary to initiate an immune response differ from the methods and means necessary to directly inhibit viral entry.

Anticipation by inherency requires that 1) the missing descriptive matter be necessarily present in the prior art reference and that 2) it would be so recognized by persons of ordinary skill in the art. *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 U.S.P.Q.2d 1746, 1749 (Fed. Cir. 1991). Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. *Hansgirg v. Kemmer*, 102 F.2d 212, 40 U.S.P.Q. 665, 667 (CCPA 1939). The Berzofsky patent

fails to provide any teaching that the processes disclosed therein would result in anything more than the initiation of an immune response against viral antigens. One of ordinary skill would not extrapolate from the reference that the method might be used for the additional purpose of directly inhibiting viral entry.

The teachings of the cited reference fail to expressly or inherently anticipate the subject matter of the instant application. Claims to a direct inhibition of viral entry are novel and non-obvious over references addressing immunological methods.

PETITION FOR EXTENSION OF TIME

Pursuant to 37 C.F.R. § 1.136(a), Applicants petition for an extension of time of one month to and including April 6, 2000 in which to respond to the Final Office Action dated September 28, 1999. Pursuant to 37 C.F.R. § 1.17, a check in the amount of ($205.00) is enclosed, which includes the process fee ($55.00) for a one-month extension of time and the fee for filing the Appeal Brief ($150.00). If the check is inadvertently omitted, or should any additional fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason relating to the enclosed materials, or should an overpayment be included herein, the Assistant Commissioner is authorized to deduct or credit said fees from or to Fulbright & Jaworski Deposit Account No. 50-1212/UTSC:538/HAS.

X. CONCLUSION

As demonstrated by the above arguments, the rejections asserted by the PTO have been entered in error. Removal of the rejections and allowance of the application is respectfully requested.

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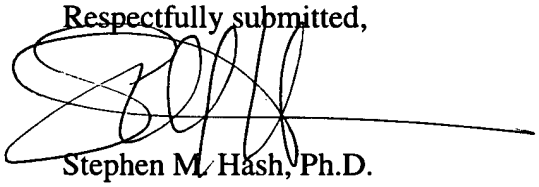
Respectfully submitted,



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